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Common Genes Contribute to Depressive Symptoms and Heart Rate Variability: The Twins Heart Study

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Depression and reduced heart rate variability (HRV) are predictors of coronary artery disease (CAD), and highly correlated with each other. However, little is known to what extent this correlation can be explained by common genetic components. We examined 198 middle-aged male twins (121 monozygotic and 77 dizygotic) from the Vietnam Era Twin Registry. Current depressive symptoms were assessed using the Beck Depression Inventory-II and HRV was assessed on 24-hour electrocardiographic Holter recordings. Five frequency domain variables were used, including ultra low frequency (ULF), very low frequency (VLF), low frequency (LF), high frequency (HF) and total power (TPow). Structural equation modeling was used to estimate shared genetic effects for depressive symptoms and the HRV frequency domains. Both depressive symptoms ($h^2=.5$) and all measurements of HRV showed high heritability ($h^2=.43-.63$). A significant inverse correlation was found between depressive symptoms and all HRV indices except LF and HF, with the highest coefficient (r) for TPow ($r = -.24$, $P = .01$) and ULF ($r = -.24$, $P = .01$). Bivariate genetic modeling revealed significant genetic correlations between depressive symptoms and TPow ($r_A = -.21$, $P = .04$), as well as ULF ($r_A = -.23$, $P = .02$). Of the total covariance between depressive symptoms and these two HRV indices, over 80% was due to the same genetic factors. In conclusion, depressive symptoms are associated with decreased HRV and this association is due, in large part, to a shared genetic effect. These results suggest that a common neurobiological dysfunction links depression and autonomic dysregulation.

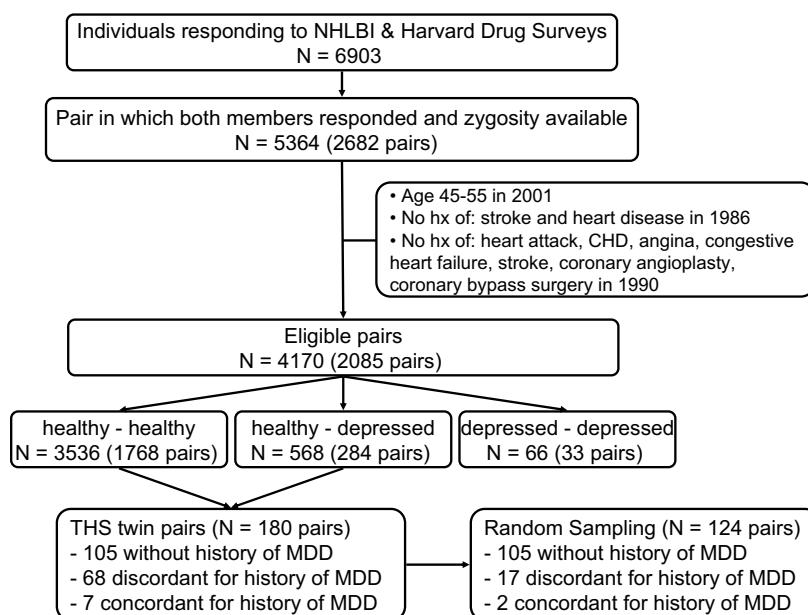
Keywords: depressive symptoms, heart rate variability, twin study, common genes

Depression has been associated with increased risk of morbidity and mortality in patients with coronary artery disease (CAD; Lett et al., 2004). However, the pathophysiologic mechanisms linking depression and cardiovascular disease have not been fully understood. Dysregulation of the autonomic nervous system (ANS) has been proposed as a plausible explanation (Carney et al., 2005b), since disordered autonomic function with increased sympathetic tone has been found in patients with depression, as evidenced by elevated plasma and urinary catecholamine levels (Veith et al., 1994).

A commonly used method for assessing autonomic modulation of cardiac function is to measure heart rate variability (HRV), a noninvasive assessment of beat-to-beat heart rate fluctuations over time. Low HRV reflects excessive cardiac sympathetic or inadequate parasympathetic modulation (Pagani et al., 1986), and is a strong, independent predictor of mortality in patients with acute myocardial infarction (Bigger et al., 1992) as well as in general population (Dekker et al., 2000; Tsuji et al., 1996). Major depression and depressive symptoms are associated with decreased HRV, both in patients with CAD (Carney et al., 2001; Vigo et al., 2004) and in community subjects (Udupa et al., 2007; van der Kooy et al., 2006). However, the causal direction of this association remains unclear. Clinical studies have shown that HRV increases in depressed patients following pharmacological antidepressant treatment and cognitive-behavioral

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**Figure 1**

Flow chart showing the construction of the Twins Heart Study sample.

therapy (Khaykin et al., 1998). On the other hand, stimulation of the left cervical vagus nerve has been recently found to be useful in treating depression (Nemeroff et al., 2006). These results underscore the possible bidirectional association between depression and cardiac autonomic dysregulation.

An alternative explanation for the link between depression and HRV is that these two phenotypes share a common genetic substrate. Both depression and HRV are in large part under genetic control (Kupper et al., 2004; Levinson, 2006); therefore it is plausible that their association could result from shared genes, perhaps genes implicated in a common neurobiological pathway. Discovery of such common genetic substrate may point towards a common etiological pathway and improve our understanding of the mechanisms underlying neural-cardiac interactions. The purposes of the current study were to estimate the heritability of depressive symptoms and HRV indices in a sample of middle-aged male twins and to examine in detail the role of genetic influences on their correlation using structural equation modeling.

Materials and Methods

Subjects

The Twins Heart Study (THS) included 360 middle-aged male twins from the Vietnam Era Twin (VET) Registry (Goldberg et al., 2002), who were all born between 1946 and 1956 (>90% of the twins in the VET registry fall into this range). The methods of construction of this sample are shown in Figure 1 and were also described before (Su et al., 2008). Briefly, the twins were free of a self-reported previous diagnosis of cardiovascular disease based on survey data

collected in 1990 (Scherrer et al., 2003), including a previous diagnosis of myocardial infarction, coronary heart disease, angina, congestive heart failure or stroke, or previous coronary angioplasty or coronary bypass surgery. From this group, we randomly sampled two groups of twin pairs: one group included twin pairs discordant for major depressive disorder (MDD), where one member of the pair had a lifetime history of MDD and the other did not; the second group of twins included pairs where neither had a history of MDD. As shown in Figure 1, the sampling design of THS, with over-representation of MDD-discordant pairs and MDD-free pairs, could bias heritability estimation of depressive symptoms. In order to minimize such bias, we further randomly selected twin pairs from THS to approximate the MDD distribution in the VET Registry. Specifically, for the current study we included all the THS pairs without MDD history, and randomly selected 17 MDD-discordant twin pairs and 2 MDD-concordant twin pairs (Figure 1). This procedure yielded a sample for analysis with a MDD distribution similar to the original sample, i.e., 105 normal twin pairs (85%), 17 MDD-discordant twin pairs (13%) and 2 MDD-concordant twin pairs (2%). After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Institutional Review Board of the Emory University School of Medicine.

Assessment of Depressive Symptoms

We administered the Beck Depression Inventory-II (BDI-II), a standardized scale providing a continuous measure of depressive symptoms (Beck et al., 1996). This self-report instrument has been used extensively in

community samples and has satisfactory test-retest and internal consistency reliability (Osman et al., 2004).

Measurement of Heart Rate Variability

Twins wore an ambulatory ECG (Holter) monitor (GE Marquette SEER digital system) for 24 hours. Both twins in a pair were studied at the same time and their recording times, schedule and activity level during the recording were matched. All activity was restricted to quiet walking in the clinical facility or around the campus. Participants were instructed to refrain from smoking and drinking alcohol or coffee during the recording. HRV data were analyzed following published methodology (Bigger et al., 1992; Lampert et al., 2003). The power spectrum was integrated over four discrete frequency bands: ultra low frequency (ULF) < .0033 Hz; very low frequency (VLF) .0033 to .04 Hz; low frequency (LF) .04 to .15 Hz; high frequency (HF) .15 to .40 Hz, and total power (TPow) < .40 Hz. All HRV data were log-transformed for analysis. Twins with > 20% interpolation or < 18 recorded hours were excluded from the analysis.

Other Measurements

A medical history and a physical exam were obtained from all twins. Weight and height were used to calculate body mass index (BMI). Physical activity was assessed by means of a modified version of the Baecke Questionnaire of Habitual Physical Activity used in the Atherosclerosis Risk in Communities Study (Richardson et al., 1995); this is a 16-question instrument documenting level of physical activity at work, during sports and non-sports activities. The global physical activity score was used in the analysis. Cigarette smoking was classified into current versus never or past smoker.

Statistical Analysis

In initial descriptive analyses we compared means and percents of study factors between MZ and DZ twins. Correlations between depressive symptoms, HRV indices and other covariates were assessed using Pearson correlations for continuous variables and Spearman correlations for categorical variables. A priori specified covariates were further adjusted, including age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD. *P* values were corrected for the correlation between co-twins using generalized estimating equations (GEE). These analyses were performed using the statistical software package SAS, Inc. version 9.0 (SAS, Inc., Cary, NC).

To estimate the relative contributions of genetic and environmental influences on the depressive symptoms and HRV indices, structural equation models were constructed using the software package Mx (Neale et al. 2003). The twin design allows separation of the observed phenotypic variance into underlying additive genetic variance (A), common environmental variance shared by a twin pair (C), and environmental variance specific to individuals (E). The assumptions under these models were that MZ twins share 100%

of their genes whereas DZ twins share 50% on average. Shared environmental effects were assumed to be 100% for both MZ and DZ twins since they were reared together, while unique environmental effects were not shared between the siblings for either MZ or DZ twins. A greater similarity of phenotype(s) in MZ twins as compared with DZ twins, as indicated by a higher correlation in MZ than DZ twins, suggests a genetic effect.

The univariate genetic models were fit to estimate the heritability for depressive symptoms and each HRV parameter. To examine the hypotheses that genetic and environmental factors contribute to the correlations of depressive symptoms and HRV, bivariate models fitting the association between these two traits were then examined. The phenotypic variation for each trait was decomposed into genetic variance (A), shared environmental variance (C) and unshared (or unique) environmental variance (E) (Figure 2). The correlation between the two traits was similarly partitioned into components resulting from A, C and E (Figure 2). Models were fit by the method of maximum likelihood. A series of nested submodels were each tested for their goodness of fit against a saturated model that placed no constraints on the elements of the estimated monozygotic and dizygotic twin variance/covariance matrices. The difference in likelihood values between a submodel and the full model is approximately distributed as χ^2 , with degrees of freedom (df) equal to the difference in df between the submodel and the full model. Akaike's Information Criterion (AIC) was also used to evaluate the relative fit of the various models. A lower AIC indicates a better balance between goodness of fit and parsimony. The 95% CIs around parameter estimates were examined to evaluate whether the genetic, shared environmental, or unique environmental contributions to depressive symptoms and HRV indices differed significantly from. Analyses were repeated after adjusting for covariates including age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD.

Results

Of the 248 THS twins, 198, including 80 pairs and 38 singletons (resulting from exclusion of the co-twin) had usable ambulatory ECG data (18 hours or more of recording with at least 80% noninterpolated intervals). The mean age (\pm SD) was 55 years (\pm 2.86), and age ranged from 47 to 60 years. None of the study factors showed a significant difference between MZ and DZ twins (Table 1).

Physical activity was significantly correlated with depressive symptoms and all HRV indices, except for HF. BMI was only significantly associated with LF. Current smokers had lower HRV and higher depressive symptom scores (Table 2). Depressive symptoms were significantly associated with decreased HRV indices including TPow ($r = -.24$, $P = .01$), ULF ($r = -.24$, $P = .01$) and VLF ($r = -.19$, $P = .01$), but not

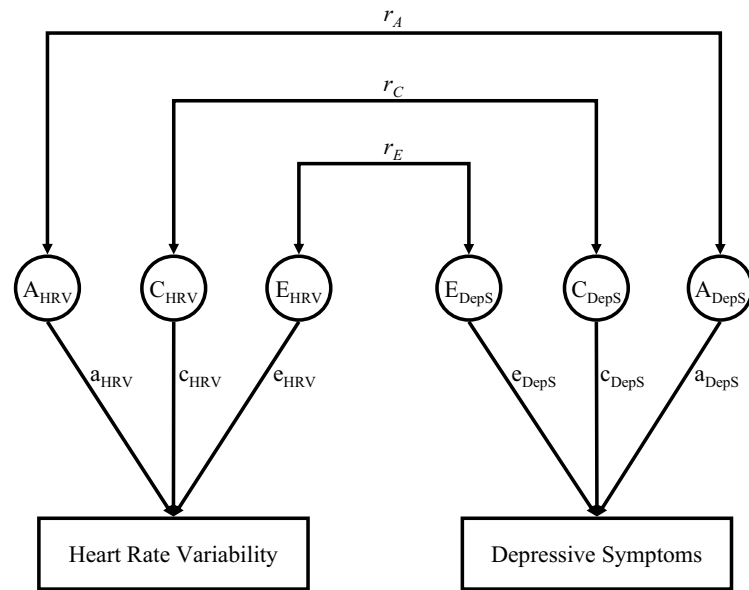


Figure 2
A schematic diagram for the bivariate biometric model examining the relationship between heart rate variability (HRV) and depressive symptoms (DepS). Factors influencing HRV and DepS include genetic factors (A), shared environment (C), and unique environment (E). Correlations between these factors across traits are represented as r_A , r_C , and r_E respectively.

with LF ($r = -.12$, $P=.07$) and HF ($r = -.08$, $P=.06$). After adjusting for potential confounding factors including age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD, the association between BDI and HRV was slightly attenuated but remained statistically significant for TPow ($P = .02$) and ULF ($P = .03$). Thus, the subsequent bivariate genetic modeling focused on BDI, TPow and ULF.

For all HRV indices and depressive symptoms, the correlations in MZ twins were consistently higher than those in DZ twins, indicating genetic influence (Table 3). This was confirmed by univariate analysis.

The best-fitting models for all traits included only genetic and unique environmental contributions. Moderate to high heritability were estimated for all HRV indices (43–63%). For depressive symptoms, the heritability was estimated at 50% (95% CI 26–68%) and other variance was explained by the unique environmental factors. After adjusting for age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD, the heritability estimations were slightly decreased but the overall results remained similar (data not shown). Further adjustment for antidepressant use did not change the results.

Table 1
Cardiovascular Risk Factors, Depressive Symptoms and Heart Rate Variability in Monozygotic (MZ) and Dizygotic (DZ) Twins

	MZ twins ($n = 121$)	DZ twins ($n = 77$)
Mean age, years	54.3 ± 2.9	54.9 ± 2.7
Body mass index, kg/m ²	28.6 ± 3.7	3.0 ± 5.0
Physical activity (Baecke scores)	7.49 ± 1.5	7.48 ± 1.5
Current smokers, %	18.2	15.6
History of coronary artery disease, %	4.96	7.79
Taking beta-blocker medications, %	7.44	3.90
Taking anti-depressant medications, %	11.6	1.4
Depressive symptoms (BDI scores)	4.24 ± 5.94	4.90 ± 7.06
Index of heart rate variability		
ln Total Power, ms ²	9.45 ± .47	9.50 ± .51
ln Ultra Low Frequency, ms ²	9.12 ± .51	9.20 ± .54
ln Very Low Frequency, ms ²	7.65 ± .52	7.64 ± .60
ln Low Frequency, ms ²	6.72 ± .67	6.68 ± .73
ln High Frequency, ms ²	5.37 ± .90	5.41 ± .92

Note: SD, standard deviation; ln, logarithm transformation; BDI, beck depression inventory.

Table 2

Phenotypic Correlations Between Covariates, Heart Rate Variability and Depressive Symptoms

	ln TPow	ln ULF	ln VLF	ln LF	ln HF	BDI scores
Age	.07	.07	.14	.02	-.07	-.19
Body mass index	-.06	-.04	-.06	-.16	-.04	-.03
Physical activity	.20	.16	.27	.19	.09	-.29
Current smoking	-.16	-.17	-.13	-.12	.03	.25
History of CAD	-.08	-.06	-.12	-.06	-.11	-.03
Beta-blocker medications	.02	.02	.02	-.04	.01	.06
BDI scores	-.24	-.24	-.19	-.12	-.08	—

Note: ln, logarithm transformation; TPow, total power; ULF, ultra low frequency; VLF, very low frequency; LF, low frequency; HF, high frequency; CAD, coronary artery disease; BDI, beck depression inventory

P values are derived from generalized estimating equation models, and < .05 shown in bold.

Table 3

Correlations of MZ and DZ Twins and Univariate Model Fitting Results for Heart Rate Variability and Depressive Symptoms

	MZ	DZ	a ² (95% CI)	e ² (95% CI)
ln TPow	.65	.03	.63 (.41 – .77)	.37 (.23 – .59)
ln ULF	.59	.09	.59 (.37 – .74)	.41 (.26 – .63)
ln VLF	.60	.12	.57 (.35 – .73)	.43 (.27 – .65)
ln LF	.52	.12	.43 (.20 – .61)	.57 (.39 – .80)
ln HF	.63	.31	.56 (.37 – .70)	.44 (.30 – .63)
BDI	.49	.16	.50 (.26 – .68)	.50 (.32 – .74)

Note: ln, logarithm transformation; TPow, total power; ULF, ultra low frequency; VLF, very low frequency; LF, low frequency; HF, high frequency; BDI, beck depression inventory
a² = additive genetic variance component (heritability), e² = unique environmental variance component.

Bivariate model fitting for the relationship between depressive symptoms and HRV, including TPow and ULF, is shown in Table 4. For all models, the common environmental components (C) could be dropped from the full model (ACE) without a significant reduction in fit ($P > .5$). However, if the genetic components (A) was dropped, the submodel was significantly worse than the ACE model ($P < .01$). Thus, both before and after adjustment for covariates, the best fitting bivariate models for the relationship between depressive symptoms and HRV were the AE models.

As shown in Table 5, the parameter estimations for the best fitting AE models suggested that there were significant genetic correlations between TPow and BDI ($r_A = -.21$, 95 CI%, $-.38$ to $-.02$), as well as ULF and BDI ($r_A = -.23$, 95 CI%, $-.40$ to $-.04$). Of the overall covariance between depressive symptoms and TPow, about 80% was due to the same genetic factors. Similarly, for depressive symptoms and ULF, about 90% of the covariance was influenced by the same genetic factors. After adjustment for covariates, the genetic correlations between depressive symptoms and HRV indices remained statistically significant or at least borderline (Table 5).

Discussion

In a sample of predominantly healthy twins we found that both depressive symptoms and HRV indices were

highly heritable. The association between depressive symptoms and reduced HRV is due, in large part, to a shared genetic pathway, suggesting that a common neurobiological dysregulation links depression and autonomic dysfunction.

Reduced HRV is associated with depression or depressive symptoms, both in patients with CAD (Carney et al., 2001; Vigo et al., 2004), and in community subjects (Udupa et al., 2007; van der Kooy et al., 2006). Our findings are similar to previous studies in which associations between HRV and depression were stronger for lower frequency domains (Carney et al., 2001). In addition, the lower frequency bands ULF and VLF, which account for 90% of the total power in a 24-hour period, have been most strongly associated with mortality in post-myocardial infarction patients (Bigger et al., 1992; Carney et al., 2005a).

Although several distinct HRV frequency bands of the heart period power spectrum are commonly measured, the relative contributions of sympathetic and parasympathetic activity to these HRV indices cannot be precisely specified. ULF, VLF, and LF power are all influenced by both sympathetic and parasympathetic systems, whereas HF is largely thought to reflect parasympathetic modulation (Taylor et al., 1998). In addition, ULF and VLF may also be affected by day-night changes in heart period, especially when activity is controlled; these changes, in turn, may be influenced by autonomic activity (1996; Roach et al., 2004).

Table 4

Goodness of Fit Statistics From the Bivariate Genetic Models for Heart Rate Variability and Depressive Symptoms, Before and After Adjustment for Covariates

Traits	Model	−2LL	df	−2LL	df	P value	AIC
Unadjusted							
ln TPow & BDI	Full model (ACE)	1521.9	385				751.8
	Drop all C (AE model) *	1521.9	388	.00	3	.99	745.8
	Drop all A (CE model)	1535.1	388	13.3	3	.004	759.1
	Drop all A and C (E model)	1557.3	391	35.4	6	< .001	755.3
ln ULF & BDI	Full model (ACE)	1554.7	385				784.7
	Drop all C (AE model) *	1554.7	388	.00	3	.99	778.7
	Drop all A (CE model)	1566.4	388	11.7	3	.009	79.4
	Drop all A and C (E model)	1587.3	388	32.6	6	< .001	805.3
Adjusted†							
ln TPow & BDI	Full model (ACE)	1463.9	381				701.9
	Drop all C (AE model) *	1463.9	384	.005	3	.99	695.9
	Drop all A (CE model)	1473.8	384	9.83	3	.02	705.8
	Drop all A and C (E model)	1495.0	387	31.0	6	< .001	721.0
ln ULF & BDI	Full model (ACE)	1496.5	381				734.5
	Drop all C (AE model) *	1496.5	384	.02	3	.99	728.5
	Drop all A (CE model)	1505.4	384	8.90	3	.03	737.4
	Drop all A and C (E model)	1525.4	387	28.9	6	< .001	751.4

Note: −2LL, −2 times log-likelihood; df, degree of freedom; , difference; AIC, Akaike's Information Criterion
ln, logarithm transformation; TPow, total power; ULF, ultra low frequency; BDI, beck depression inventory
A, additive genetic component; C, shared environmental component; E, unique environmental component

* The best-fitting model

†Adjusted for age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD.

Unlike the current study, previous investigations have seldom controlled for physical activity. In our study, activity during the recording was matched between twins, and we also adjusted for habitual physical activity in the analysis.

Previous twin and family studies have shown an important role of genetic factors in the liability to depression and in the regulation of cardiac autonomic activity. Heritability is estimated to account for 37–75% of the liability for major depressive disorder. Depressive symptoms show a more modest but significant genetic influence (Kendler et al., 2006; Silberg et al., 1990; Su et al., 2008). Studies of HRV in families and twins suggest that a considerable part of the variation in these indices can be explained by genetic factors, with heritability estimations between .13 and .71 for a variety of HRV indices (Singh et al., 2001; Wang et al., 2005). Overall, the results of the present study are in agreement with these previous findings.

This is the first study to examine whether depression and disordered autonomic function share a common underlying mechanism, such as a common genetic vulnerability. By constructing bivariate genetic models in MZ and DZ twins, our study provided a unique opportunity to determine the extent to which the observed correlation between depression and HRV is caused by common genes. Both before and after adjusting for covariates, significant genetic correlations were observed between depressive symptoms and

TPow and ULF. Of the total genetic variation of depression and HRV indices, about 80–90% was due to the same genetic factors. These results indicate that common genes contribute substantially to the covariation of these two phenotypes.

Common genes that may be involved in regulation of both depression and autonomic function include those in the hypothalamus-pituitary-adrenal (HPA) axis, or in the sympathetic, parasympathetic and serotonin pathways, which have been related to depression and may be relevant for autonomic regulation (Belmaker & Agam, 2008; Levinson, 2006). For example, hypothalamic corticotrophin-releasing hormone (CRH) was found to be increased in medically healthy patients with depressive symptoms; it, in turn, leads to sympathetic activation with increased norepinephrine production and decreased HRV (Grippe & Johnson 2002). Recent studies have observed a higher prevalence of certain alleles and haplotypes in the CRH receptor gene and glucocorticoid receptor gene in major depression patients than controls (Liu et al. 2006; van Rossum et al. 2006). In addition, genetic polymorphisms in serotonergic genes, such as serotonin transporter, serotonin receptors and monoamine oxidase A, have been associated with depression (McCaffery et al., 2006). Although the relationship of these polymorphisms with autonomic dysfunction is not known, recent experimental studies in both human and animals have indicated that

Table 5

Parameter Estimates from the Best Fitting Bivariate Models for Heart Rate Variability and Depressive Symptoms, Before and After Adjustment for Covariates

Traits	a^2 (95% CI)	e^2 (95% CI)	r_A (95% CI)	r_E (95% CI)
Unadjusted				
ln TPow	0.64 (.42 – .77)	0.36 (.23 – .58)	–0.21 (–.38 – –.02)	–0.05 (–.20 – .06)
BDI	0.52 (.28 – .69)	0.48 (.31 – .72)		
ln ULF	0.61 (.39 – .75)	0.39 (.25 – .61)	–0.23 (–.40 – –.04)	–0.02 (–.17 – .10)
BDI	0.52 (.28 – .69)	0.48 (.31 – .72)		
Adjusted*				
ln TPow	0.62 (.40 – .76)	0.38 (.24 – .60)	–0.19 (–.36 – .002)	–0.02 (–.17 – .11)
BDI	0.45 (.20 – .63)	0.55 (.37 – .80)		
ln ULF	0.6 (.38 – .74)	0.4 (.26 – .62)	–0.22 (–.39 – –.04)	0.01 (–.13 – .14)
BDI	0.46 (.21 – .64)	0.54 (.36 – .79)		

Note: ln, logarithm transformation; TPow, total power; ULF, ultra low frequency; BDI, beck depression inventory; CI, confidence interval

a^2 , additive genetic variance component (heritability); e^2 , unique environmental variance component

r_A , genetic correlation; r_E , unique environmental correlation

* Adjusted for age, BMI, physical activity, smoking status, beta-blocker medication and history of CAD

impaired serotonergic function may affect the variability of heart rate (Hildreth et al., 2008).

There are several limitations to this study. First, our study is cross-sectional, thus limited in the ability to discern the temporal order between depression and HRV. However, based on our results, the covariation of these two phenotypes is due in large part to a common genetic precursor rather than being a cause-effect relationship. Second, our sample is derived from a twin registry of military veterans, where the members may be in some ways different from the general population of similarly aged American males. Third, our analyses included only male twins, thus one should be cautious to extend our results to females.

In conclusion, we found that both depressive symptoms and HRV indices are heritable and the association between them is due, in large part, to a shared genetic effect. These results suggest that a common neurobiological dysfunction links depression and autonomic dysregulation. Our data provide important insight into the mechanisms underlying neural-cardiac interactions and point to the importance of uncovering common genetic variants that may be implicated in both depression and HRV. These results have substantial implications for our understanding of the link between depression and autonomic dysfunction, suggesting that genetic susceptibility may play an important role.

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